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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,706	08/24/2000	Keith V. Wood	341.005US1	3329

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/645,706	WOOD ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11,12,14,15,18,20,21,24-39,41-45,47,60-64 and 67-80* is/are pending in the application.

4a) Of the above claim(s) *64,75 and 79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11,12,14,15,20,21,24-39,41-45,47,60-63,67-74 and 76-78* is/are rejected.

7)☒ Claim(s) *18 and 80* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 7, 8, 10, 13, 16, 17, 19, 22, 23, 40, 46, 48-59, 65 and 66 have been canceled. Claims 1-6, 9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45, 47, 60-64, 67, 68 and newly presented claims 69-80 are still at issue and are present for examination.

Applicants' arguments filed on 6/7/04, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 64, 75, and 79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 11/18/02.

Applicants further traverse the withdrawal of Claim 64 by arguing "claim 64 depends on claim 63, which were both assigned to Group I, the elected group of claims. Therefore, claim 64, directed to a vector which includes a 1) gene of interest and 2) backbone sequences which contain a synthetic nucleic acid molecule that does not encode a polypeptide, should be examined with the elected group of claims and not withdrawn from consideration for being directed to subject matter in a non-

elected group. However this is not persuasive because the action of 9/10/02 also included a requirement for an election of a species of a synthetic nucleic acid for examination on the merits. Applicants elected SEQ ID NO:9 (i.e., a nucleic acid encoding the GRver5.1 luciferase) as the species for examination. The subject matter of claim 64 **does not** encompass the elected species and thus this claim was properly withdrawn from consideration. Similarly new claims 74 and 79 also do not encompass the elected species and are also withdrawn from consideration.

Claims 1, 47, 63, 67, 68, and 73 objected to because of the following informalities: the word "and" should be deleted after "transcription factor binding sequences". Appropriate correction is required.

Applicant is advised that should claim 34 be found allowable, claim 62 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Each of these claims limit original claim 1 to those synthetic nucleic acids which encode the same protein as the parent wild type nucleic acid and thus are of identical scope.

Claims 1-6, 9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45, 47, 60-63, and 67-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (from which claims 2-6, 9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45 and 60-62 depend), 47, 63, 67, 68, 72 and 73 are vague and indefinite in the recitation of "a reduced number of transcription factor binding sequences" and/or "a reduced number of intron splice sites, poly(A) addition sites and promoter sequences" as without knowing all the possible sequences which are considered to be transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences such a calculation is impossible as one could never obtain a count of the number of such sequence in any reference nucleic acid. While there are clearly art defined specific sequences within each of these categories, each of them is an open-ended group of sequences which includes many unknown members. Clearly while many transcription factors and their

associated binding sequences are known in the art, new members are being added frequently such that the scope of the claims would change.

Applicants argue that the terms "transcription factor binding sequences", "intron splice sites", "poly(A) addition sites" and "promoter sequences" are conventional in the art. This is acknowledged. However, in the art these terms define a group of sequences related by function. The art does not define clearly **what** sequences are included in the group. Since applicants invention requires a skilled artisan to **quantify** the number of such sequences it is imperative that the artisan know explicitly what sequences are to be included and what sequences are not so one can in fact count them. While the art clearly defines **some** specific sequences which fall into each group (for example AAUAAA as a polyadenylation sequence) many other sequences may have the same function and not all such sequences are known and taught by the art. Applicants further argue that there is nothing intrinsically wrong in using functional language, defining something by what it does rather than by what it is, in drafting patent claims and courts have recognized the practical necessity for the use of functional language. This is not persuasive because the examiner never stated that the use of

functional language is always indefinite but that in the instant situation that this language is indefinite as the claims recite **a reduced number** of these sites requiring that a skilled artisan be capable of counting them. This is only possible if the sites can be identified by some means besides experimental testing for the function as the number of subsequences of any reporter gene is so enormous that this could not be achieved. The specification describes using a computer to scan the sequence of a gene for specific subsequences but does not identify a specific group to be scanned for.

Claim 63 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This claim is directed to a genus of variant vectors comprising a synthetic nucleic acid having 3 fewer transcription regulatory sequences relative to a parent nucleic acid molecule.

The specification does not contain any disclosure of the function of all nucleic acids within the scope of the claimed genera. The genera of nucleic acids that comprise these above

nucleic acids are large and variable with the potentiality of encoding many different proteins and vector sequences. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims. The specification discloses only a few species of the claimed genera which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants argue that the specification teaches several representative species of luciferase mutants with amino acid substitutions relative to a wild type sequence, which representative proteins have reporter activity. This is acknowledged and the rejection of most claims which now recite genes encoding reporter proteins which are structurally homologous to a parent reporter protein and retain reporter activity has been withdrawn. However, the rejection is

maintained for the instant claim in which these limitations are not present.

Claims 1-6, 9, 11, 12, 14, 15, 20-21, 24-33, 35-39, 41-45, 47, 60, 61, 63, 67-70, 72-74, 77 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant of a parent DNA molecule encoding a reporter polypeptide identical to a reporter polypeptide encoded by said parent DNA, having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 under high stringency conditions and encode a polypeptide having luciferase activity, does not reasonably provide enablement for any variant DNA molecules encoding a reporter polypeptide having at least 85% identity to a wild type reporter polypeptide, having more than 25% of the codons altered and having reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 under medium stringency conditions, encode a protein having 85% identity to the polypeptide encoded by SEQ ID NO:9,

have more than 25% of the codons altered and have a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants argue that the specification teaches several representative species of luciferase mutants with amino acid substitutions relative to a wild type sequence, which representative proteins have reporter activity and that numerous substitutions have been introduced into beetle luciferases without affecting the reporter property of the substitution variants. For instance, in U.S. Patent No. 6,602,677, five mutant luciferases are disclosed that have 12, 21, 32, 37, and 37 substitutions, respectively, relative to a parent luciferase. Likewise, numerous substitutions have been introduced into other reporter proteins, such as GFP.

Applicants arguments are noted however the scope of enablement is not commensurate in scope with the claims. The vast majority of applicants claims are not limited to any particular reporter polypeptide. The extent of art guidance

with regard to regions of each reporter polypeptide which can be successfully modified while retaining reporter activity varies widely. While some such as firefly or click beetle luciferases and GFP have been extensively modified and the art provides a substantial amount of guidance for other reporter polypeptides, including many other luciferases (for example coelenterate luciferases), the amount of guidance provided by the art is highly limited at best. Furthermore, it should be noted that even for the click beetle luciferase, the most extensively modified variants in the art (i.e., U.S. Patent No. 6,602,677) those of still retain substantially more identity to the parent luciferase than the 85% identity (or ability to hybridize under medium stringency conditions) recited in applicants claims. As such the rejection is maintained for the reasons of record for the above claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter

of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9, 11, 12, 14, 15, 20, 21, 24-39, 41-45, 60-63, 67-70, 72-74, 76, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304), Donnelly et al. (WO 97/47358), Iannacone et al. and Pan et al.

Sherf et al. teach a modified firefly luciferase gene in which 14% of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells and eliminate sequences which encode transcription factor binding sites for know mammalian transcription factors including ATF, AP1, Sp1, AP2 etc. which would interfere with its "genetically neutral" behavior expected of a reporter gene. The altered gene includes at least 6 fewer transcription factor binding sites and was inserted into several mammalian expression vectors. The altered gene is transcribed and translated efficiently in mammalian host cells. The altered luciferase

differs from the variant nucleic acids of the claims in that 25% or more of the codons were not altered. Sherf et al. further disclose that similar modifications could be made to other luciferase genes including click beetle luciferase

Zolotukhin et al. teach a modified *Aequorea victoria* GFP gene in which 37% of the codons have been altered (and optionally up to even 80-90% may be altered) without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells. The optimized gene is inserted into an expression vector including a Kozak consensus sequence preceding the ATG initiation codon which optionally may include a multiple cloning site positioned between the promoter and the humanized GFP gene and/or downstream of the GFP gene. The altered gene preferably includes CTG codons encoding leucine, GTG or GTC codons encoding valine, GGC codons encoding glycine, ATC codons encoding isoleucine, CCT codons encoding proline, CGC codons encoding arginine, AGC codons encoding serine, ACC codons encoding threonine, and GGC or GGT codons encoding alanine and is transcribed and translated 5-10 times more efficiently in human cells than the wild type gene.

Donnelly et al. teach a modified hepatitis C virus core antigen gene in which 61% of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells and eliminate sequences which encode undesired sequences (such as ATTTA sequences, intron splice sites, etc.) generated by the alteration of the natural codons (see pages 17-18).

Iannacone et al. teach a modified *cry*3B gene in which 44% of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for plant host cells and eliminate sequences which would destabilize the mRNA including polyadenylation sequences and splicing sites. The altered gene includes at least 6 fewer polyadenylation sequences and was inserted into a plant expression vector including a Kozak consensus sequence preceding the ATG initiation codon. The altered gene is transcribed and translated efficiently in transgenic plants while the wild type gene is not transcribed at all.

Pan et al. teach a modified *Plasmodium falciparum* gene in which a large number of the codons have been altered without

altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells and eliminate sequences which might be detrimental to transcription and translation of the synthetic gene including sequences of promoters, poly A signals, intron splice sites and long runs of purines which might act as transcriptional termination sequences (see pages 1095). It should be noted that the elimination of undesired sequences was performed after the modification of the codon preference and thus would eliminate undesired sequences artificially introduced by the change in codons. The modified gene was successfully expressed in a variety of host cells (see page 1096) while expression of the unmodified gene has turned out to be difficult if not impossible (see page 1095).

Therefore, it would have been obvious to further modify the luciferase gene of Sherf et al. to both increase the codon preference for humans as each of Zolotukhin et al., Donnelly et al., and Pan et al. each teach modifying a large percentage of the codons of a gene to be expressed in humans and to remove potential promoter sequences, polyadenylation sites and splice sites in order to further increase its usefulness as a reporter gene in human and other mammalian cells. One would have had a

reasonable expectation of success in view of the results of Zolotukhin et al., Pan et al. and Iannacone et al. which all show that such alterations of other genes which are to be expressed in evolutionarily highly distinct organisms from those in which they evolved substantially improve the levels of expression in the new host.

Applicants argue with regard to the previous 103 rejection, that the combination of references does not disclose or suggest Applicant's invention as each reference discloses a different wav to modify the coding sequence of a gene to increase expression, i.e., Zolotukhin et al. disclose codon modification alone generally throughout a green fluorescent protein gene, Sherf et al. disclose limited and targeted modification (modifications in 20 regions of 6 to 30 bp) of a firefly luciferase sequence to introduce or remove cloning sites, alter insect codons to mammalian codons, and to remove post-translation modification sites, secondary structure, and transcription factor binding sites, and Iannaconne et al. disclose targeted modification of four regions of a toxin gene to alter Bacillus codons to plant codons, and to remove poly A sequences, ATTTA sequences and strings of A or T > 4. This is not persuasive as each of these references as teach methods of

increasing the expression of a desired gene in a host which is distinctly different than the organism from which the gene originated. As such one of skill in the art would have been motivated to combine the individual methods together in order to achieve even greater improvements. Furthermore, the additional references of Donnelly et al. and Pan et al. both show that it was known in the art to combine these individual methods as each of these references include **both** the modification of the majority of the codons of the gene of interest **and** the elimination of sequences which would interfere with transcription and/or translation.

Applicants further argue that there is no teaching in the cited art that codon modifications can introduce undesirable sequences into the synthetic gene and that codon selection can decrease the introduction of those sequences. While this is true with regard to the references used in the previous rejection, the newly cited references of Donnelly et al. and Pan et al. both show that the art recognized that this was the case as in each case, the elimination of undesired sequences was performed after the alteration of the codon preference and Donnelly et al. explicitly state on pages 17-18 when describing the methods of design of a synthetic gene "Inspect new gene

sequence for undesired sequences **generated by these codon replacements** (e.g. "ATTA" sequences, inadvertent creation of intron splice sites, unwanted restriction enzyme sites, etc.) and substitute codons that eliminate these sequences" [emphasis added]. This clearly shows that the art recognized that codon modifications can introduce undesirable sequences into the synthetic gene and that codon selection can decrease the introduction of those sequences.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652